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DIETARY FIBER AND THE RISK OF COLORECTAL CANCER AND ADENOMA IN WOMEN

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ABSTRACT

Background A high intake of dietary fiber has been thought to reduce the risk of colorectal cancer and adenoma.

Methods We conducted a prospective study of 88,757 women, who were 34 to 59 years old and had no history of cancer, inflammatory bowel disease, or familial polyposis, who completed a dietary questionnaire in 1980. During a 16-year follow-up period, 787 cases of colorectal cancer were documented. In addition, 1012 patients with adenomas of the distal colon and rectum were found among 27,530 participants who underwent endoscopy during the follow-up period.

Results After adjustment for age, established risk factors, and total energy intake, we found no association between the intake of dietary fiber and the risk of colorectal cancer; the relative risk for the highest as compared with the lowest quintile group with respect to fiber intake was 0.95 (95 percent confidence interval, 0.73 to 1.25). No protective effect of dietary fiber was observed when we omitted adjustment for total energy intake, when events during the first six years of follow-up were excluded, or when we excluded women who altered their fiber intake during the follow-up period. No significant association between fiber intake and the risk of colorectal adenoma was found.

Conclusions Our data do not support the existence of an important protective effect of dietary fiber against colorectal cancer or adenoma. (N Engl J Med 1999;340:169-76.)

THE rarity of colorectal cancer in Africa suggested to Burkitt several decades ago that the high-fiber diet of Africans was protective against colorectal cancer.[1] Since then, dietary fiber has been postulated to prevent colorectal cancer by diluting or adsorbing fecal carcinogens, reducing colonic transit time, altering bile acid metabolism, reducing colonic pH, or increasing the production of short-chain fatty acids.[2]

Despite the intuitive appeal of Burkitt's hypothesis, epidemiologic studies of a possible link between dietary fiber and colorectal cancer have been inconclusive.[3] The limited data on other dietary factors included in most studies did not permit a clear distinction to be made between the effects of fiber and those of other constituents of plant foods. Moreover, the retrospective design of these studies may have introduced recall and selection biases.

We prospectively examined the relation between fiber intake and the risk of colorectal cancer in a large cohort of women. In an earlier report based on 150 cases of colorectal cancer reported during six years of follow-up,[4] we observed a minimal inverse association that was not statistically significant. In the present analysis, we extend follow-up to 16 years in order to examine more thoroughly the influence of dietary fiber on the risk of colorectal cancer and adenoma.

METHODS

Study Cohort

The Nurses' Health Study was initiated in 1976, when 121,700 female registered nurses who were 30 to 55 years of age and residing in the United States completed a mailed questionnaire on known or suspected risk factors for cancer and coronary heart disease.[5] Since then, the women have been sent follow-up questionnaires every two years to bring information on these risk factors up to date and to identify newly diagnosed cases of cancer and other diseases. Dietary intake was first assessed in 1980, when the women completed a mailed semiquantitative food-frequency ques-

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tionnaire. For this analysis, we excluded women who left 10 or more items blank on the 1980 food-frequency questionnaire, those with implausibly high or low scores for total energy intake, and those who reported a history of cancer (except nonmelanoma skin cancer), ulcerative colitis, Crohn's disease, or a familial polyposis syndrome. After these exclusions, 88,757 women remained eligible for follow-up from 1980 through 1996.

Data on Dietary Fiber and Other Factors

The study women provided information on their smoking history, age, height, weight, level of physical activity, aspirin use, family history of colorectal cancer, and any examination by colonoscopy or sigmoidoscopy, as well as the indications for the procedure.

In 1980 the semiquantitative food-frequency questionnaire included 61 items; the 1984 questionnaire was expanded to 121 items, and the 1986 questionnaire included 136 items. For each food listed, a commonly used unit or portion size was specified and participants were asked how often, on average, they had consumed that amount of each food over the past year; there were nine possible responses. We also asked about the brand of breakfast cereal and multivitamin typically used and provided an open-ended section for foods not listed. We computed nutrient intakes by multiplying the frequency of consumption of each food by the nutrient content of the specified portions, using composition values from Department of Agriculture sources supplemented with other data, including the components of specific multivitamins and breakfast cereals.[6] Values for total dietary fiber were based on the work of Southgate and colleagues.[7] All nutrients and dietary fiber were adjusted for total energy intake by the residuals method.[8] At base line, we did not collect information on fiber supplements; on the 1994 questionnaire, fewer than 6 percent of the women were taking plantago-seed (psyllium-seed) supplements regularly.

The reproducibility and validity of these questionnaires have been documented previously.[9,10] The energy-adjusted correlation for crude intake of fiber as measured by the 1980 questionnaire and as calculated from records of dietary intake of weighed foods in 1980 was 0.61.[10] Similarly, the correlation between crude intake of fiber as reported in the 1984 questionnaire and that found in the 1980 dietary records of weighed portions was 0.56.[11] Among the chief contributors to dietary fiber, the energy-adjusted correlations between intake as reported on the 1980 questionnaire and in the dietary records were 0.71 for white bread, 0.77 for dark bread, 0.79 for cold cereal, 0.80 for apples, 0.74 for oranges, 0.79 for bananas, 0.50 for peas, 0.73 for tomatoes, 0.63 for string beans, and 0.69 for broccoli.[12]

Identification of Cases of Colorectal Cancer or Adenoma

On each questionnaire we inquired whether colon or rectal cancer had been diagnosed and, if so, requested the date of the diagnosis. For this analysis, the follow-up data were available for 96 percent of the total possible person-years. Most of the deaths in the cohort were reported by family members or the postal system in response to the follow-up questionnaires. In addition, we used the National Death Index, a highly sensitive method of identifying deaths among nonrespondents.[13] When a woman (or the next of kin) reported a diagnosis of colorectal cancer, we asked for permission to obtain medical records and pathology reports. A study physician blinded to the womens' exposure and intake data reviewed all records and extracted data on the histologic type, anatomical location, and stage of cancer. We excluded the small number of cancers that were not adenocarcinomas, as well as carcinomas in situ. This left 787 cases of invasive colorectal adenocarcinoma.

The analysis of adenomas was restricted to women who were eligible for the analysis of cancer and who reported undergoing colonoscopy or sigmoidoscopy during the study period. Because the review of medical records for cases of adenoma has been completed only through 1994, the study period for adenomas was defined as 1980 through 1994. After these exclusions, 27,530 women were eligible for this portion of the analysis. When a woman reported a diagnosis of a colorectal polyp, we obtained medical records and pathology reports. A study physician unaware of the risk-factor data reviewed all records and extracted data on the type, location, and size of the adenoma.[14] Because a sigmoidoscopic examination encompasses only the distal portion of the colon and rectum and because a substantial portion of those who underwent endoscopy had a sigmoidoscopy, we assessed only adenomas of the descending colon and rectum. Women with adenomas proximal to the descending colon were not classified as having adenoma in this analysis. This left 1012 patients with adenomas of the distal colon and rectum.

Statistical Analysis

Women were categorized according to quintiles with respect to total fiber intake and intake of specific types of fiber as computed from the 1980, 1984, and 1986 dietary questionnaires. For the primary analysis, we used incidence rates, with person-years of follow-up as the denominator. For each woman, person-years of follow-up were counted from the date of the return of the baseline questionnaire until the date of a diagnosis of colorectal cancer or death or until May 31, 1996. We used relative risk as a measure of association, defined as the incidence of colorectal cancer among study women in each quintile of fiber intake divided by the corresponding rate among the women in the lowest quintile. Age-adjusted relative risks were calculated after stratification, according to five-year age categories. Proportional-hazards models were used to adjust for multiple risk factors simultaneously. Stratified analyses were conducted to determine whether the influence of fiber intake was modified by other risk factors for colorectal cancer. All P values are two-sided.

To evaluate the influence of measurement error on our findings, we used a correction procedure that adjusts the relative risks and confidence intervals to account for errors in assessing fiber intake.[15] This procedure requires a "gold standard" for a subgroup of the women in order to calibrate the questionnaire used in the entire cohort; for this, we used detailed dietary records of weighed portions of food collected for 28 days over a 1-year period for a subgroup made up of 173 participants.[10]

RESULTS

During the 16 years of follow-up (1,408,232 person-years), we documented 787 cases of colorectal cancer among the 88,757 eligible women. Within the entire cohort, the median energy-adjusted total dietary fiber intake differed by more than a factor of 2.5 between the highest and the lowest quintiles (Table 1). Women who consumed more fiber were older, less likely to have smoked cigarettes, and more apt to exercise regularly, to have a family history of colorectal cancer, and to undergo screening endoscopy. In addition, women who reported higher fiber intake consumed less red meat and alcohol but more folate, calcium, and vitamin D.

In age-adjusted and multivariate analyses based on data from the 1980 questionnaire and 16 years of follow-up, energy-adjusted total dietary fiber intake was not significantly associated with the incidence of colorectal cancer (Table 2). Moreover, there was no relation between total dietary fiber intake and the risk of cancer in the proximal or distal colon. There was also no relation when dietary fiber was analyzed without adjustment for total energy intake (multivariate relative risk of colorectal cancer in the highest as compared with the lowest quintile, 1.17; 95 per-

TABLE 1. BASE-LINE CHARACTERISTICS OF THE STUDY COHORT.*

CHARACTERISTIC	QUINTILE OF ENERGY-ADJUSTED FIBER INTAKE				
	1 (N=17,773)	2 (N=17,803)	3 (N=17,772)	4 (N=17,747)	5 (N=17,662)
Median dietary fiber intake (g/day)	9.8±1.7	13.1±0.8	15.9±0.8	19.1±1.1	24.9±5.5
Median age (yr)	45	46	46	47	49
Former or current smoker					
Percentage of women	63	58	55	54	53
Pack-yr†	25.5	22.0	20.6	19.5	18.6
Body-mass index‡	23.6	23.7	23.7	23.7	23.7
Regular vigorous exercise (%)§	36	42	45	49	56
Regular aspirin use (%)¶	24.3	24.5	24.1	23.8	22.2
Colorectal cancer in a parent or sibling (%)	7.5	7.8	7.9	7.9	8.0
Screening endoscopy (%)‖	15.1	16.4	17.2	17.9	19.2
History of colorectal polyps (%)**	1.2	1.0	1.0	1.2	1.2
Dietary intake					
Beef, pork, or lamb as a main dish (servings/wk)	3.0	2.6	2.3	2.1	1.6
Methionine (g/day)	1.8	1.8	1.9	1.9	1.9
Folate (μg/day)	278	318	352	396	484
Alcohol (g/day)	10.1	7.2	6.4	5.9	4.9
Calcium (mg/day)	678	703	722	752	810
Vitamin D (IU/day)	278	282	286	298	315

*All values other than age have been directly standardized according to the age distribution of the cohort. Nutrient values represent mean energy-adjusted intake. Plus–minus values are medians ±SD.

†Pack-years were calculated for former and current smokers only.

‡The body-mass index is the weight in kilograms divided by the square of the height in meters.

§Regular vigorous exercise was defined as vigorous physical activity (enough to work up a sweat) on one or more days per week.

¶Regular aspirin use was defined as use on two or more days per week.

‖Screening endoscopy was included if it occurred during the study period.

**Only colorectal polyps diagnosed before the study period were included.

cent confidence interval, 0.91 to 1.51) or when we analyzed crude fiber (multivariate relative risk, 0.96; 95 percent confidence interval, 0.73 to 1.25).

Because the variation in fiber intake within the highest quintile was much greater than that within the other quintiles (Table 1), we also analyzed total fiber as a continuous variable. In multivariate analyses, each increment of 10 g per day in total fiber intake corresponded to a relative risk of colorectal cancer of 0.99 (95 percent confidence interval, 0.83 to 1.17). To evaluate extreme levels of dietary fiber consumption, we repeated our analysis after categorizing fiber intake according to energy-adjusted deciles. As compared with women in the lowest decile (median intake, 8.5 g per day), women in the highest decile (median intake, 28.5 g per day) had a relative risk of colorectal cancer of 1.01 (95 percent confidence interval, 0.71 to 1.43).

Since previous work has suggested that fiber from various food sources may be related to colorectal cancer in different ways, we computed the contributions of dietary fiber from cereals, fruits, and vegetables (Table 3). Only fruit fiber was associated with any appreciable reduction in risk (multivariate relative risk, 0.86; 95 percent confidence interval, 0.67 to 1.10), but the overall trend was not statistically significant (P=0.16). In contrast, greater consumption of vegetable fiber was associated with a significant increase in the risk of colorectal cancer (multivariate relative risk, 1.35; 95 percent confidence interval, 1.05 to 1.72; P for trend=0.004).

To examine the possibility that total dietary fiber influences the risk of colorectal cancer only after several years, we analyzed the relation between dietary fiber as assessed in 1980 and the risk of colorectal cancer from 1986 through 1996. Despite the six-year latency period, greater dietary fiber intake was not associated with a reduction in the risk of colorectal cancer (multivariate relative risk, 1.00; 95 percent confidence interval, 0.72 to 1.38).

Among the women who returned the 1980 questionnaire, 65,186 women also completed a longer and more detailed dietary questionnaire in 1986. In an analysis based on the 1986 questionnaire and the incidence of cancer from 1986 through 1996, no significant trend was observed between energy-adjusted dietary fiber intake and the risk of colorectal cancer (multivariate relative risk, 0.98; 95 percent confidence interval, 0.72 to 1.34). We also examined the risk of colorectal cancer according to the mean

TABLE 2. RELATIVE RISK OF COLORECTAL CANCER ACCORDING TO TOTAL DIETARY FIBER INTAKE IN 1980.*

VARIABLE	QUINTILE OF ENERGY-ADJUSTED DIETARY FIBER					P VALUE FOR TREND
	1	2	3	4	5	
Median fiber intake (g/day)	9.8	13.1	15.9	19.1	24.9	
All colorectal cancers						
No. of cases	158	145	160	159	165	
Age-adjusted RR (95% CI)	1.0	0.81 (0.64–1.04)	0.89 (0.70–1.13)	0.84 (0.66–1.07)	0.89 (0.70–1.12)	0.16
Multivariate RR (95% CI)	1.0	0.90 (0.71–1.13)	0.96 (0.75–1.21)	0.93 (0.72–1.19)	0.95 (0.73–1.25)	0.59
Colon cancer						
No. of cases	98	101	125	107	105	
Age-adjusted RR (95% CI)	1.0	0.91 (0.67–1.23)	1.10 (0.82–1.47)	0.92 (0.68–1.23)	0.89 (0.66–1.19)	0.20
Multivariate RR (95% CI)	1.0	1.04 (0.78–1.39)	1.26 (0.94–1.68)	1.06 (0.77–1.45)	1.04 (0.74–1.46)	0.88
Cancer in proximal colon						
No. of cases	50	52	66	66	47	
Age-adjusted RR (95% CI)	1.0	0.96 (0.62–1.49)	1.11 (0.73–1.69)	1.18 (0.78–1.77)	0.84 (0.54–1.30)	0.20
Multivariate RR (95% CI)	1.0	1.07 (0.71–1.60)	1.34 (0.90–2.00)	1.34 (0.88–2.04)	1.00 (0.61–1.61)	0.96
Cancer in distal colon						
No. of cases	48	49	59	41	58	
Age-adjusted RR (95% CI)	1.0	0.86 (0.56–1.31)	1.09 (0.74–1.61)	0.69 (0.45–1.06)	0.93 (0.62–1.38)	0.64
Multivariate RR (95% CI)	1.0	1.01 (0.67–1.53)	1.18 (0.80–1.78)	0.79 (0.50–1.26)	1.08 (0.67–1.72)	0.99
Rectal cancer						
No. of cases	35	22	21	30	35	
Age-adjusted RR (95% CI)	1.0	0.59 (0.36–1.03)	0.55 (0.32–0.93)	0.77 (0.47–1.24)	0.81 (0.51–1.30)	0.54
Multivariate RR (95% CI)	1.0	0.54 (0.32–0.89)	0.47 (0.27–0.79)	0.68 (0.41–1.12)	0.63 (0.37–1.08)	0.37

*RR denotes relative risk, and CI confidence interval. Multivariate relative risks have been adjusted for age (in 5-year categories), smoking status (0, 1 to 15, 16 to 25, 26 to 45, or >45 pack-years), body-mass index (in quintiles), regular vigorous exercise (≥1 vs. <1 day per week), regular aspirin use (≥2 vs. <2 times per week), colorectal cancer in a parent or sibling (yes or no), screening endoscopy during the study period (yes or no), history of colorectal adenomas (yes or no), consumption of beef, pork, or lamb as a main dish (<1 serving per month, 1 to 3 per month, 1 per week, 2 to 4 per week, or ≥5 per week), alcohol-consumption status (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), and quintiles of energy-adjusted intake of folate, methionine, calcium, and vitamin D. The numbers of colon and rectal cancers may not equal the total numbers of colorectal cancers because in some cases the specific site of the cancer was unknown. Proximal colon denotes the segment from the cecum to the splenic flexure, and distal colon denotes the segment from the splenic flexure to the rectosigmoid junction. In the calculation of the relative risks, the group with the lowest intake of dietary fiber served as the reference group.

dietary fiber intake in 1980, 1984, and 1986 and found no association (multivariate relative risk for the highest as compared with the lowest quintile, 1.00; 95 percent confidence interval, 0.69 to 1.47).

We assessed the effect of consistent fiber intake over a six-year induction period. After classifying the women according to their fiber intake in 1980, we excluded those who subsequently increased or decreased their fiber intake by more than one quintile as reported on either the 1984 or the 1986 questionnaire. Among women who maintained a consistent level of fiber intake from 1980 through 1986, dietary fiber intake was not associated with a reduction in the risk of colorectal cancer from 1986 through 1996 (Table 4). Similarly, neither consistent consumption of fiber from cereal nor consistent intake of vegetable fiber was associated with a reduction in the incidence of colorectal cancer.

We found no evidence of an inverse association between fiber and colorectal cancer in any subgroup defined by age, family history of colorectal cancer, aspirin use, physical activity, body-mass index, cigarette smoking, or total intake of fat (Table 5), or by intake of alcohol, red meat, methionine, calcium, or vitamin D (data not shown). We did find an inverse relation between total dietary fiber intake and the incidence of colorectal cancer among women in the lowest third of the group with respect to folate consumption. Within this stratum, the inverse association was restricted to fruit fiber (relative risk for the highest as compared with the lowest quintile of fruit fiber, 0.59; 95 percent confidence interval, 0.35 to 0.99; P for trend=0.06).

To evaluate possible distortion of our findings by higher rates of screening endoscopy among women who consumed more dietary fiber, we repeated our analysis after stratification according to whether or not women had undergone screening endoscopy during the study period; we found no inverse relation between fiber intake and colorectal cancer in either stratum (Table 5). We also repeated our analysis after excluding women whose cancers may have been detected incidentally or only by screening (Dukes' stages A and B). When we restricted the outcome to more advanced lesions in this way, the relative risk for the highest as compared with the lowest quintile with respect to fiber intake was 0.94 (95 percent confidence interval, 0.62 to 1.44).

Errors in assessing dietary fiber intake could have biased the relative risks. When we adjusted for age and total energy intake, the relative risk of colorectal cancer associated with a 10-g increase in daily total dietary fiber intake was 1.00 (95 percent confidence interval, 0.89 to 1.13). After adjustment for errors in

TABLE 3. RELATIVE RISK OF COLORECTAL CANCER ACCORDING TO DIETARY INTAKE OF FIBER FROM VARIOUS SOURCES IN 1980.*

TYPE OF FIBER AND VARIABLE	QUINTILE OF ENERGY-ADJUSTED FIBER INTAKE					P VALUE FOR TREND
	1	2	3	4	5	
Cereal fiber						
Median intake (g/day)	1.0	1.8	2.5	3.3	4.8	
No. of cases of colorectal cancer	161	143	153	161	169	
Multivariate RR (95% CI)	1.0	0.90 (0.71–1.13)	0.95 (0.75–1.19)	0.99 (0.79–1.24)	1.00 (0.79–1.27)	0.69
Fruit fiber						
Median intake (g/day)	0.8	1.9	3.1	4.5	7.2	
No. of cases of colorectal cancer	150	148	169	155	165	
Multivariate RR (95% CI)	1.0	0.94 (0.74–1.18)	1.03 (0.82–1.29)	0.88 (0.69–1.12)	0.86 (0.67–1.10)	0.16
Vegetable fiber						
Median intake (g/day)	2.7	4.0	5.3	6.8	10.0	
No. of cases of colorectal cancer	150	147	144	164	182	
Multivariate RR (95% CI)	1.0	0.98 (0.78–1.23)	0.98 (0.78–1.25)	1.13 (0.89–1.43)	1.35 (1.05–1.72)	0.004

*RR denotes relative risk, and CI confidence interval. Multivariate relative risks have been adjusted for age (in 5-year categories), smoking status (0, 1 to 15, 16 to 25, 26 to 45, or >45 pack-years), body-mass index (in quintiles), regular vigorous exercise (≥1 vs. <1 day per week), regular aspirin use (≥2 vs. <2 times per week), colorectal cancer in a parent or sibling (yes or no), screening endoscopy during the study period (yes or no), history of colorectal adenomas (yes or no), consumption of beef, pork, or lamb as a main dish (<1 serving per month, 1 to 3 per month, 1 per week, 2 to 4 per week, or ≥5 per week), alcohol-consumption status (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), and quintiles of energy-adjusted intake of folate, methionine, calcium, vitamin D, and the two other food sources of fiber. In the calculation of the relative risks, the group with the lowest intake of dietary fiber from a given source served as the reference group.

TABLE 4. RELATIVE RISK OF COLORECTAL CANCER AMONG WOMEN WITH CONSISTENT FIBER INTAKE.*

TYPE OF FIBER AND VARIABLE	QUINTILE OF ENERGY-ADJUSTED FIBER INTAKE					P VALUE FOR TREND
	1	2	3	4	5	
Total fiber						
No. of cases of colorectal cancer	38	39	30	43	45	
Multivariate RR (95% CI)	1.0	1.11 (0.69–1.77)	1.00 (0.58–1.70)	1.16 (0.68–1.96)	1.31 (0.74–2.32)	0.35
Cereal fiber						
No. of cases of colorectal cancer	33	30	27	30	39	
Multivariate RR (95% CI)	1.0	0.94 (0.57–1.56)	1.09 (0.64–1.86)	1.00 (0.59–1.70)	1.23 (0.73–2.08)	0.41
Fruit fiber						
No. of cases of colorectal cancer	47	33	36	46	38	
Multivariate RR (95% CI)	1.0	0.62 (0.31–1.24)	0.71 (0.36–1.40)	0.65 (0.33–1.28)	0.66 (0.33–1.32)	0.31
Vegetable fiber						
No. of cases of colorectal cancer	33	37	38	35	39	
Multivariate RR (95% CI)	1.0	1.15 (0.50–2.63)	1.97 (0.89–4.38)	1.58 (0.70–3.58)	1.22 (0.50–2.98)	0.39

*Subjects whose intake of total fiber or any type of fiber on either the 1984 or the 1986 questionnaire varied from that specified on the 1980 questionnaire by more than one quintile were excluded from the analysis of that type of fiber. (Total numbers of subjects for types of fiber therefore differ from one another and do not sum to the number of subjects in the analysis of total fiber.) The remaining subjects were categorized according to intake in 1980. Only participants who completed the 1980, 1984, and 1986 dietary questionnaires were eligible. RR denotes relative risk, and CI confidence interval. Multivariate relative risks have been adjusted for age (in 5-year categories), smoking status (0, 1 to 15, 16 to 25, 26 to 45, or >45 pack-years), body-mass index (in quintiles), regular vigorous exercise (≥1 vs. <1 day per week), regular aspirin use (≥2 vs. <2 times per week), colorectal cancer in a parent or sibling (yes or no), screening endoscopy during the study period (yes or no), history of colorectal adenomas (yes or no), consumption of beef, pork, or lamb as a main dish (<1 serving per month, 1 to 3 per month, 1 per week, 2 to 4 per week, or ≥5 per week), alcohol-consumption status (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), and quintiles of energy-adjusted intake of folate, methionine, calcium, vitamin D, and the two other food sources of fiber (for analyses of fiber from cereal, fruits, and vegetables). In the calculation of the relative risks, the group with the lowest intake of dietary fiber from a given source served as the reference group.

TABLE 5. RELATIVE RISK OF COLORECTAL CANCER ACCORDING TO DIETARY FIBER INTAKE IN SUBGROUPS DEFINED BY SELECTED VARIABLES.*

VARIABLE	NO. OF CASES	QUINTILE OF ENERGY-ADJUSTED TOTAL DIETARY FIBER INTAKE					P VALUE FOR TREND
		1	2	3	4	5	
		relative risk					
Age							
≤50 yr	327	1.0	0.84	0.99	1.02	1.12	0.50
>50 yr	460	1.0	0.95	0.93	0.88	0.88	0.44
Family history of colorectal cancer							
Yes	115	1.0	1.25	0.92	1.05	0.92	0.66
No	672	1.0	0.84	0.96	0.90	0.96	0.97
Regular aspirin use†							
Yes	154	1.0	0.93	1.00	0.98	0.87	0.71
No	633	1.0	0.89	0.94	0.92	0.97	0.97
Regular physical exercise‡							
Yes	318	1.0	0.80	0.87	0.88	0.88	0.82
No	469	1.0	0.95	1.00	0.95	1.00	0.96
Body-mass index§							
≤21	183	1.0	0.65	1.06	0.94	0.94	0.82
22–24	279	1.0	1.00	0.97	1.09	0.99	0.73
≥25	325	1.0	0.97	0.89	0.79	0.94	0.91
Smoking status							
0 pack-yr	351	1.0	0.87	1.02	1.04	0.93	0.94
≤30 pack-yr	265	1.0	0.82	0.82	0.78	0.92	0.85
>30 pack-yr	171	1.0	1.02	1.01	0.91	1.02	0.94
Total fat¶							
≤64 g/day	255	1.0	0.83	0.87	0.94	1.01	0.56
65–75 g/day	275	1.0	0.91	1.06	1.05	0.92	0.90
≥76 g/day	257	1.0	0.87	0.87	0.70	1.08	0.70
Folate intake¶							
≤226 μg/day	250	1.0	0.69‖	0.93	0.80	0.36‖	0.07
227–362 μg/day	296	1.0	1.00	1.10	0.91	0.87	0.30
≥363 μg/day	241	1.0	1.40	0.80	1.17	1.32	0.29
Screening endoscopy during the study							
Yes	280	1.0	0.82	1.09	1.13	1.01	0.71
No	507	1.0	0.94	0.90	0.82	0.95	0.64

*Multivariate relative risks have been adjusted for age (in 5-year categories), smoking status (0, 1 to 15, 16 to 25, 26 to 45, or >45 pack-years), body-mass index (in quintiles), regular vigorous exercise (≥1 vs. <1 day per week), regular aspirin use (≥2 vs. <2 times per week), colorectal cancer in a parent or sibling (yes or no), screening endoscopy during the study period (yes or no), history of colorectal adenomas (yes or no), consumption of beef, pork, or lamb as a main dish (<1 serving per month, 1 to 3 per month, 1 per week, 2 to 4 per week, or ≥5 per week), alcohol-consumption status (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), and quintiles of energy-adjusted intake of folate, methionine, calcium, and vitamin D. In each case, the stratification variable was excluded from the model. In the calculation of the relative risks, the groups with lowest intake of dietary fiber served as the reference group.

†Regular aspirin use was defined as use on two or more days per week.

‡Regular physical exercise was defined as vigorous physical activity (enough to work up a sweat) on one or more days per week.

§The body-mass index is the weight in kilograms divided by the square of the height in meters.

¶Total fat and folate have been adjusted for total energy intake.

‖$P<0.05$ for the comparison with the lowest quintile.

measuring fiber and total energy intake, the relative risk associated with a 10-g increase was still 1.00 (95 percent confidence interval, 0.74 to 1.36).

We also assessed the relation between fiber intake and the risk of distal colorectal adenomas among 27,530 women who reported undergoing colonoscopy or sigmoidoscopy between 1980 and 1994. There was no reduction in the risk of colorectal adenoma with increasing dietary intake of total, cereal, fruit, or vegetable fiber, even when we restricted our analysis to women who had undergone endoscopy before 1980 and had been determined at that time to be free of polyps (Table 6).

DISCUSSION

In this large, prospective cohort study, we found no evidence that dietary fiber reduces the risk of colorectal cancer. This result is unlikely to be due to imprecise measurement of fiber intake or to biased ascertainment of colorectal cancers. Our prospective

TABLE 6. RELATIVE RISK OF DISTAL COLORECTAL ADENOMA ACCORDING TO DIETARY FIBER INTAKE IN 1980.*

VARIABLE	QUINTILE OF ENERGY-ADJUSTED FIBER INTAKE					P VALUE FOR TREND
	1	2	3	4	5	
All women with adenomas						
Total dietary fiber						
No. of cases/total no. of women	194/4861	190/5259	216/5542	200/5757	212/6111	
Multivariate RR (95% CI)	1.0	0.98 (0.79–1.21)	1.07 (0.86–1.33)	0.95 (0.76–1.20)	0.91 (0.71–1.16)	0.36
Cereal fiber						
No. of cases/total no. of women	196/5220	216/5374	212/5476	192/5615	196/5845	
Multivariate RR (95% CI)	1.0	1.14 (0.93–1.39)	1.09 (0.89–1.33)	0.95 (0.77–1.17)	0.92 (0.75–1.14)	0.14
Fruit fiber						
No. of cases/total no. of women	194/4845	204/5245	188/5585	222/5842	204/6013	
Multivariate RR (95% CI)	1.0	1.04 (0.85–1.28)	0.90 (0.73–1.11)	1.00 (0.81–1.24)	0.85 (0.68–1.06)	0.12
Vegetable fiber						
No. of cases/total no. of women	204/5203	211/5423	196/5578	195/5621	206/5705	
Multivariate RR (95% CI)	1.0	1.01 (0.83–1.23)	0.92 (0.74–1.13)	0.89 (0.71–1.10)	0.89 (0.71–1.12)	0.19
Women with adenomas and previously negative endoscopic results†						
Total dietary fiber						
No. of cases/total no. of women	27/878	23/1021	26/1002	29/1179	35/1292	
Multivariate RR (95% CI)	1.0	0.88 (0.49–1.58)	1.10 (0.60–2.00)	1.04 (0.56–1.95)	1.17 (0.61–2.22)	0.51

*RR denotes relative risk, and CI confidence interval. Multivariate relative risks have been adjusted for age (in 5-year categories), smoking status (0, 1 to 15, 16 to 25, 26 to 45, or >45 pack-years), body-mass index (in quintiles), regular vigorous exercise (≥1 vs. <1 day per week), regular aspirin use (≥2 vs. <2 times per week), colorectal cancer in a parent or sibling (yes or no), screening endoscopy during the study period (yes or no), history of colorectal adenomas (yes or no), servings of beef, pork, or lamb as a main dish (<1 per month, 1 to 3 per month, 1 per week, 2 to 4 per week, or ≥5 per week), alcohol-consumption status (abstinence, history of greatly reduced consumption, or <15, 15 to 30, or >30 g per day), and quintiles of energy-adjusted intake of folate, methionine, calcium, vitamin D, and the two other food sources of fiber (for analyses of fiber from cereal, fruits, and vegetables). In the calculation of relative risks, the group with the lowest intake of dietary fiber from a given source served as the reference group.

†This category comprises women who underwent endoscopy before 1980, with negative results.

study design precluded bias attributable to differential recall of intake by women with and without cancer. Variation in fiber intake over time was not a factor, because our results remained unchanged when we excluded women who substantially altered their fiber intake during the first six years of observation.

By means of a food-frequency questionnaire, we were able to examine the influence of fiber at recommended intakes (25 to 35 g per day),[16] which are considerably higher than the mean dietary fiber intake in the U.S. adult population (13.3 g per day).[17] The fact that, in this cohort and others, strong inverse associations between fiber intake and the incidence of symptomatic diverticular disease,[18] coronary heart disease,[19] hypertension,[20,21] and non-insulin-dependent diabetes mellitus[22] were observed in studies using the same questionnaire suggests that we used a physiologically relevant measure of fiber intake.

We cannot rule out a weak association between fiber intake and colorectal cancer, an effect of fiber early in life, or an influence of the consumption of more than 30 to 35 g of fiber per day. However, the last association would imply a nonlinear relation between fiber intake and the risk of colorectal cancer, which is not suggested by the previous retrospective studies.

Evidence for the hypothesis that fiber intake is related to the risk of colon cancer has been inconclusive. A meta-analysis of case–control studies demonstrated a combined odds ratio of 0.58 for colon cancer in the highest as compared with the lowest quintile of fiber intake.[23] However, when this analysis was restricted to studies that used validated dietary questionnaires and incorporated qualitative data into estimates of nutrient intakes, the relative-risk estimates for colorectal cancer associated with consumption of more dietary fiber were closer to 1.00.[24] In five large, prospective studies,[25-29] inverse associations between the intake of fiber and the risk of colon cancer were weak or nonexistent. Using a limited dietary questionnaire, Thun et al. did find a significant inverse relation between the intake of "citrus fruit, vegetable, and high-fiber grains" and colon cancer, although dietary fiber intake was not specifically analyzed.[30] Moreover, three placebo-controlled, randomized trials found no significant reduction in

the incidence of colorectal tumors among subjects who received fiber supplementation.[31-33] A recent prospective study of 16,448 U.S. men also did not find a significant association between the dietary intake of total, cereal, or vegetable fiber and colorectal adenomas, although a slight reduction in risk was observed with increasing intake of fruit fiber.[34]

Many previous studies assessed a limited number of potential confounders. One of these, folate, occurs in plant foods and may protect against colon cancer.[3,35,36] In our analysis, adjustment for folate intake did attenuate the weak association between fiber and colorectal cancer.

The significant positive association between the intake of vegetable fiber and the risk of colorectal cancer was unexpected. In a prospective study of 41,837 middle-aged women, Steinmetz et al. observed an increased risk of colon cancer with greater consumption of cruciferous vegetables and potatoes.[29] In our own study, however, we found no link between vegetable-fiber intake and the risk of adenoma.

There are cogent reasons for increasing fiber intake, particularly the inverse association with coronary heart disease observed in many studies.[19,37] However, we found no evidence to support the hypothesis that total dietary fiber intake is protective against colorectal cancer or adenoma.

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